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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/308,725	01/13/2000	Ajit Lalvani	077529.0112	6572

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EXAMINER	
CHEN, STACY BROWN	
ART UNIT	PAPER NUMBER
1648	

NOTIFICATION DATE	DELIVERY MODE
11/05/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	09/308,725	LALVANI ET AL.	
	Examiner	Art Unit	
	Stacy B. Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 May 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and response filed August 22, 2008 have been entered. Claims 40-61 and new claims 62 and 63 are pending and under examination.

Response to Amendment

2. The objection to claims 47 and 69 is withdrawn in view of Applicant's amendment.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 40-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Surcel *et al.* (*Immunology*, 1994, 81:171-176, "Surcel"), in view of Sørensen *et al.* (*Infection and Immunity*, 1995, 63(5):17170-1717, "Sørensen"), and Hagiwara *et al.* (*AIDS Research and Human Retroviruses*, January 20, 1996, 12(2):127-133, "Hagiwara"). The rejection is reproduced below for convenience.

Surcel discloses Th1/Th2 profiles in tuberculosis, based on the proliferation and cytokine response of blood lymphocytes to mycobacterial antigens. "Proliferation and cytokine production profiles by blood mononuclear cells in response to in vitro stimulation with mycobacterial antigens were compared in patients with active tuberculosis and in sensitized healthy people", page 171, abstract. Surcel uses the ELISPOT assay to measure effector T-cells that produce IFN-γ. Surcel's method uses freshly isolated PBMCs from patients with active tuberculosis. The cells are incubated in 96-well plates for 72 hours, in the presence of antigen, before transfer to anti-IFN-γ antibody-coated nitrocellulose-bottomed plates in the presence of a mycobacterial antigen. The cells were then incubated for 20 hours and subsequently enumerated (page 172, second column, last three paragraphs). Surcel is silent on the ESAT-6 mycobacterial antigen.

However, Sørensen discloses the discovery of a low-molecular-mass T-cell antigen secreted by *Mycobacterium tuberculosis*. Sørensen teaches that ESAT-6 is a 6-kDa early secretory antigenic target. Sørensen

discloses that native and recombinant ESAT-6 elicited a high release of IFN-γ from T-cells isolated from memory-immune mice challenged with *M. tuberculosis* (abstract).

It would have been obvious to use ESAT-6 as the activating peptide in Surcel's ELISPOT method. One would have been motivated to use ESAT-6 because it is a T-cell epitope. Surcel's method is aimed at studying the relationships between epitope specificity and T-cell function (page 172, first column, first paragraph). One of ordinary skill in the art would have been motivated to use Sørensen's antigen as the activating antigen in order to understand the relationship between the ESAT-6 specificity and T-cell function. One would have had a reasonable expectation of success based on Sørensen's disclose that ESAT-6 elicited a high release of IFN-γ from T-cells isolated from memory-immune mice challenged with *M. tuberculosis*.

Surcel's measurement of IFN-gamma producing T-cells involves incubation of T-cells in the presence of a T-cell-activating peptide for, what is reasonably deduced from the context of the protocol, 72 hours (page 172, second column, fourth full paragraph). The incubation of T-cells with T-cell activating peptide for 72 hours would allow memory T-cells to proliferate, thus the measurement of IFN-gamma producing T-cells would include both the memory T-cells and effector T-cells. This measurement of both memory and effector T-cells is not the instantly claimed invention's method of measuring only effector T-cells. However, Hagiwara teaches that ELISPOT results are divergent when studying PBMC that have been cultured and stimulated *in vitro*. While Hagiwara's disclosure is directed to cytokine production in HIV patients, the same concept applies to Surcel's ELISPOT. Hagiwara teaches that since the type and amount of cytokine produced *in vitro* can be altered by the culture conditions employed, inconsistent results from such studies are not unexpected (page 131, first column). Hagiwara chose an alternative strategy, which was to study cells actively secreting cytokines *in vivo* with an incubation time of 6 hours. Hagiwara's technique monitored the pattern of cytokines produced by cells participating in ongoing immune responses in HIV-infected individuals (see Hagiwara, page 128).

It would have been obvious to incorporate Hagiwara's teachings into Surcel's method. Surcel's method is intended for measuring effector T-cells (active tuberculosis versus sensitized healthy controls, see Surcel's abstract). One would have been motivated to use fresh T-cells in Surcel's method in view of Hagiwara's teachings about how the type and amount of cytokine produced *in vitro* can be altered by the culture conditions employed and that inconsistent results from such studies are not unexpected. Given this teaching one of ordinary skill in the art would have been motivated to reduce inconsistent results by using fresh T-cells, rather than the cells used by Surcel that were cultured *in vitro* prior to the ELISPOT assay. One would have had a reasonable expectation of success that the use of fresh T-cells in Surcel's method would have worked because Hagiwara's method uses fresh T-cells in an ELISPOT assay.

With regard to peptides of 7-12 amino acid residues in length (T-cell activating peptides), it would have been obvious to use a peptide of this length. Epitopes are known to be short peptides; methods of determining epitopes are known and routinely practiced. When given a particular protein, the ordinary artisan can readily determine epitopes, both antibody epitopes and T-cell epitopes. It is well within the ability of the ordinary artisan to identify and produce peptides comprising epitopes of interest regardless of their size/length.

With regard to the intracellular pathogen being HIV, Surcel and Sørensen do not teach the diagnosis or monitoring of HIV infection. However, it would have been obvious to diagnosis/monitor HIV infection using Surcel's method. One would have been motivated to do so by the need felt in the world for treating HIV infection, as evidenced by Hagiwara, or any other disease. Given that ELISPOT assays are generally applicable to any desired peptide of interest, one would reasonably expect that T-cells would be activated by T-cell epitopes of HIV, and that levels of IFN-gamma would be detected if present.

With regard to the limitation that the individual has been immunized with a vaccine, the claim (claim 50) does not specify what vaccine is used for immunization. Most individuals in developed countries are immunized for various diseases, including TB (the BCG vaccine). Thus, the samples used by Surcel/Sørensen/Hagiwara are most likely from individuals that have been immunized at some point in their lives prior to sampling.

Therefore, the invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

4. Applicant's arguments have been carefully considered but fail to persuade. Applicant's substantive arguments are primarily directed to the following:

- Applicant outlines seven key concepts seminal to the claimed invention, and that knowledge of each concept and the interplay of each concept is required to arrive at the invention. Applicant notes that Hagiwara and Sørensen do not teach any of the seven concepts, and Surcel arguably teaches the 5th concept: ELISPOT is a sensitive method able to enumerate responsive peptide-specific T cells *in vitro*.
  - In response to Applicant's arguments, the Office has considered the seven concepts outlined in the response. However, the knowledge and application of all seven concepts is not required to arrive at the claimed invention. There is no requirement that obviousness must be established by following the same thought processes that Applicant used.
- Applicant argues that the 4th concept (selective detection of pathogen-specific effector T cells could provide a dynamic surrogate marker for the presence of, or recent infection by, pathogen in a host) as applied to intracellular pathogens was not known prior to Applicant's invention.
  - In response to Applicant's argument, the claims do not require the determination of the presence of or recent infection by a pathogenic agent. The claims encompass the monitoring of an existing infection. Regardless, Hagiwara's technique monitored the pattern of cytokines produced by cells participating in ongoing immune responses in HIV-infected individuals (see Hagiwara, page 128),

which is reasonably understood by one of skill in the art to indicate that if cells are detected that are participating in an ongoing immune response, then there must be an infection (page 131, bridging paragraph between columns 1 and 2).

- Applicant asserts that if one were to combine the teachings of Surcel, Hagiwara and Sørensen, one would arrive at an assay methodology that explores Th1/Th2 profiles in PBMC by measuring the response of T cells to ESAT-6 following short periods of incubation. Applicant argues that the instant invention goes beyond this by focusing on the characteristics of effector cells and using that information as an endpoint for the diagnosis and/or monitoring of infectious agents in humans. Applicant argues that Surcel and Hagiwara do not teach or suggest diagnosis or monitoring of infection. With regard to Surcel, Applicant asserts that Surcel's only compares profiles of Th1/Th2 cytokine production in patients with active TB and in sensitized healthy controls. Applicant points to Surcel's discussion (page 175) as evidence that, given the lack of substantial differences between infection and control individuals' IFN-γ levels, one would not have been motivated to use Surcel's method for diagnosis and/or monitoring of infection. With regard to Hagiwara, Applicant argues that Hagiwara's assay method is measuring immune function, but cannot differentiate between different causes of immunodeficiency. Applicant concludes that Hagiwara's method does not teach diagnosis of HIV-AIDS.
  - In response, with regard to Surcel, Surcel discloses that method by examining Th1/Th2 profiles in tuberculosis patients, based on the proliferation and cytokine response of blood lymphocytes to mycobacterial antigens. Surcel's interest in

cytokine response in patients that are actively infected or sensitized is at least a method of monitoring an infection. With regard to Hagiwara, the measurement of immune function is at least considered monitoring an infection. Lacking a specific definition in the specification as to what is encompassed by "monitoring infection", the term encompasses a broad concept and relates to the observation of any aspect of an infection. Further, the rejection is based on a combination of teachings. With Hagiwara's teachings, one would have been motivated to improve the sensitivity of Surcel's method, as outlined in the rejection above.

- Applicant argues that Surcel does not appreciate the subset of effector T cells. Applicant goes on to argue that Hagiwara does not teach or suggest that IFN-γ production *in particular* is influenced by the different culture conditions. Applicant argues that the Office's reliance on this teaching by Hagiwara is not about divergent results as it relates to IFN-γ levels, rather the divergent results are with respect to prior inconsistent results between laboratories concerning the relative levels of the collective Th1 and Th2 cytokine responses associated with disease progression in HIV-infected patients. (Applicant also notes that those results in the prior art were obtained using ELISA, not ELISPOT). Further, Applicant asserts that Hagiwara's use of a shorter incubation time resulted in no change in IFN-γ levels amongst HIV-infected patients with differing disease severity.
  - In response, the Office has already recognized that Surcel does not appreciate the subset of effector T cells, thus the reliance on Hagiwara's disclosure of studying cells actively secreting cytokines in vivo with ELISPOT (page 131, bridging

paragraph between columns 1 and 2). Hagiwara does teach that cytokine-producing cell frequencies were observed between normal controls and patients with HIV, though no significant differences/trends were observed in patients with increasingly severe disease. Note that the claims broadly encompass the monitoring of an infection, not differentiating between stages of disease severity.

- With regard to the divergent results discussed by Hagiwara, the Office recognizes that those results are with respect to different experimental approaches and different laboratories. However, it is important to note Hagiwara's conclusion about those divergent results, which remains that Hagiwara chose the sensitive and specific ELISPOT assay to detect and enumerate PBMC secreting cytokines *in vivo*. The key idea here is that Hagiwara chose to use fresh cells as opposed to *in vitro*-stimulated cells, which measured effector T cell cytokine production.

▪ Applicant argues that Surcel teaches away from the claimed invention because Surcel discloses the incubation of fresh PBMCs for 72 hours prior to the ELISPOT assay. Applicant asserts that this is evidence that confirms that the prior art generally believed that IFN-γ ELISPOT assays require culturing T-cells in the presence of antigen for long periods.

- In response to Applicant's argument, the Office is aware that the incubation time used by Surcel exceeds 24 hours. As outlined in the rejection of record, this deficiency is noted and thus the Hagiwara reference is relied upon for its teachings regarding the use of fresh cells and an incubation time of 6 hours.

Conclusion

5. No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30), alternate Fridays off,. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Stacy B. Chen/
Primary Examiner, TC1600